

EXAMINATION OF THE CONSEQUENCES OF VARIOUS ANESTHETIC AGENTS ON
AUDITORY EVOKED POTENTIAL RECORDINGS

Capstone Project

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Abstract

Neurophysiologic intraoperative monitoring (NIOM) has been widely used during surgical procedures in hopes of preserving cranial nerve function and achieving better postoperative outcomes for patients. Audiologists have contributed greatly to the field of NIOM for many years. Many pharmacological agents used to induce sedation and anesthesia, along with a variety of other factors, such as gender, age, and body temperature changes that occur during surgery have been shown to impact auditory evoked potential recordings. Knowledge of the various effects of anesthesia can better prepare audiologists to recognize and correct for changes that may occur as a result of anesthetics used during surgery. Therefore, a single reference of normative data pertaining to anesthesia should be developed as a source for audiologists pursuing or practicing a career in NIOM. Expert knowledge of anesthetics and their effects on evoked potentials will improve intraoperative patient care and strengthen the audiologist's claim to the field of NIOM.

Dedication

This document is dedicated first and foremost to God in whom all things are possible, for giving me the strength and resources to complete such a feat; to my incredible parents who have unyieldingly supported me both financially and emotionally throughout my seemingly endless eight- year trek through college. No words could express how truly grateful I am for the most selfless, patient, faith-filled parents in the world; to my beautiful daughter, Hadley, whose smile got me through each and every day; and to all of Hadley's babysitters, Aunt Tracie, Uncle Joe, Aunt Kallie, Grandma, Pap, Bopchie, Gagie, and Aunt Celena, without whom the time put into this document would not have been possible. Thank you all for your unfailing commitment to help me finish my degree.

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Chapter 1: Introduction

Neurophysiologic intraoperative monitoring (NIOM) of cranial nerve activity has been widely used during surgical procedures to assess the functional integrity of the nervous system in hopes of preserving cranial nerve function and achieving better postoperative outcomes for patients (Edwards & Kileny, 2005). Many procedures performed by head and neck surgeons, otologists, and neurotologists involve the exposure of cranial nerves, particularly the auditory nerve (AN), putting these structures at risk for iatrogenic injury (Marcus et al., 2003). As a result, the field of audiology has contributed to the subspecialty area of intraoperative neurophysiologic monitoring by performing a variety of clinical tests to assist in the preservation of the AN and surrounding cranial nerves (Edwards & Kileny, 1998). Audiologists perform tests including electrocochleography (ECoG), designed to reveal immediate changes in cochlear function and the auditory brainstem response (ABR) (Edwards & Kileny, 1998).

Clinically, the ABR can be used to measure hearing sensitivity in order to estimate behavioral auditory thresholds when these cannot be measured by traditional methods, such as hand-raising, due to the age or developmental status of the patient. The ABR can also be used as a measure of neural synchrony, to assess the integrity of the AN and auditory brainstem neurons (Norrix et al., 2012). For normal developmentally functioning adolescents and adults, ABR recordings can be

performed under ideal non-invasive, quiet conditions. However, infants, children, and adults with developmental disorders or neuromuscular disease, and those undergoing surgical procedures may require sedation, anesthesia, or both. Consequently, many pharmacological agents used to induce sedation and anesthesia have been shown to impact auditory evoked potential recordings in animals (Ruebhausen et al., 2012; Stronks et al., 2010; van Looij et al., 2004), as well as in humans (Norrix et al., 2012; Manninen et al., 1985; Dubois et al., 1982.) Along with a variety of other factors, such as gender, age, and temperature changes that occur during surgery, various anesthetic drugs have been linked to reductions in ABR amplitude (Stronks et al., 2010), as well as increases in neural conduction time (Dubois et al., 1982; Thorton et al., 1983; Manninen et al., 1985; Markand et al., 1987; Schwender et al., 1995) resulting in delayed ABR absolute and interpeak latencies (Norrix et al., 2012). Because pharmacological drugs used to induce sedation and anesthesia have been shown to alter the physiologic state of the animal and human, precautionary measures should be taken to ensure that the validity of auditory evoked potential recordings is not compromised during surgical procedures.

Furthermore, knowledge of the various effects of anesthesia can better prepare audiologists performing intraoperative neurologic monitoring to recognize and correct for changes that occur in auditory evoked potential recordings and ultimately improve short and long-term outcomes for patients. The purpose of the current review is to provide a detailed overview of anesthetic agents that have been shown to influence auditory evoked potential recordings and to outline their effects

to better prepare audiologists interpreting sedated ABR recordings or performing NIOM in recognizing and correcting for changes that can occur as a result of anesthesia.

Chapter 2: Auditory Evoked Responses and their Contribution to Neurophysiologic Intraoperative Monitoring

The chief purpose of monitoring auditory evoked potentials during surgery is to reduce the risk of injury to the eighth cranial nerve (CN VIII) (Møller, 2011). Surgeries that can jeopardize the health of the intact CN VIII include vestibular schwannoma resection, microvascular decompression to relieve trigeminal neuralgia, hemifacial spasm, glossopharyngeal neuralgia (Grundy, 1983; Møller & Janetta, 1983), and operations on CN VIII in patients with tinnitus and disabling positional vertigo (Møller & Møller, 1989). Preservation of auditory function has improved over time due not only to advancements in surgical techniques, but also through the introduction of intraoperative neurophysiologic monitoring of the AN (Colletti et al., 1994; Silverstein et al., 1984; Fisher, 1989; Linden et al., 1988; Kuroki & Møller, 1995; Møller et al., 1994).

Auditory Component of Eighth Cranial Nerve

The auditory nerve plays a vital role within the auditory system. It functions to carry electrical impulses from the cochlea to the brainstem. Once auditory information has been coded within the cochlea it passes through the AN and onto the brain. Along the way, frequency and intensity characteristics of sounds are coded by the AN. AN fibers are tonotopically organized with high-frequency fibers located on the outermost portion of the nerve, the mid-frequencies located medially

to the high-frequency fibers, and low-frequency fibers located on the innermost portion of the nerve, thus preserving the tonotopicity established in the cochlea. AN fibers are connected to hair cells that run from the basal to the apical end of the cochlea and are spatially organized from high to low frequencies. Frequency is coded by place and firing rate characteristics of the AN fibers. Low frequencies are represented by low firing rates and high frequencies by high firing rates. Phase-locking capabilities of the AN allow it to lock onto cycles of sound waves causing the AN to fire synchronously with auditory stimuli. Intensity is also coded at the level of the AN. This is done using the number of fibers involved (more for higher intensities) and the firing rate of the nerve fibers, which is greater for high frequency sounds (Musiek & Baran, 2007).

Vestibular Component of Eighth Cranial Nerve

The other component of the CN VIII, the vestibular component, also plays a fundamental role in human sensory perception. Afferent fibers of the vestibular portion of CN VIII are located within the internal auditory canal near the entrance of CN VIII into the cerebellopontine angle (CPA) (Brodal, 1981). The vestibular labyrinth consists of five neural structures that detect head acceleration. These consist of three semicircular canals and two otolith organs. Two types of hair cells exist in the peripheral vestibular system. Afferent information travels from these hair cells located in the vestibular labyrinth ipsilaterally through one of two branches of the vestibular portion of CN VIII. The superior branch innervates the horizontal and anterior semicircular canals as well as the utricle otolith organ. The inferior vestibular nerve innervates the posterior semicircular canal along with the

sacculle otolith organ (Naito et al., 1995). Damage to CN VIII can manifest with both auditory and vestibular symptoms. Therefore, preservation of the integrity of CN VIII after injury or infection is important not only for maintaining auditory function, but for maintaining vestibular function as well.

Non-surgical Injury to Auditory Nerve

In addition to surgical injury for which NIOM can be used, AN fibers are vulnerable to damage by infection, disease, trauma, and medication. The main clinical pathology of CN VIII is the acoustic neuroma, which is most often a vestibular schwannoma, arising from the Schwann cells surrounding the sheath of CN VIII (House et al., 1997). These benign tumors can be dangerous because they can grow largely into the CPA and lie in close proximity to the brainstem (Lustig & Jackler, 1977). These tumors first approach the outside of the AN, causing damage to high-frequency fibers, which is why high-frequency hearing loss is one of the initial signs of an acoustic neuroma (Johnson, 1977). CN VIII tumors disrupt the function of the AN by slowing or preventing nerve impulses that travel along its axons. Reducing the speed of these impulses can cause dys-synchrony and impair the transmission of complex sounds across the nerve. This will also lead to latency delays of the ABR, or the complete loss of ABR waves. Another form of schwannoma is neurofibromatosis. Neurofibromatosis type 2 (NF2) is characterized by bilateral cochleovestibular schwannomas and progressive hearing loss. In addition to schwannomas, other tumor types including lipomas and meningiomas, can affect the AN and where the nerve enters the brainstem at the CPA.

Although tumors of the AN are the most prominent disorder of the AN,

vascular and viral lesions can also result in AN dysfunction (Møller, 2000). Cysts and aneurysms, as well as other disease processes including cochlear neuronitis, diabetic cranial neuropathy, and auditory neuropathy/ dys-synchrony can compromise the function of the AN. Although rare, inflammation of CN VIII can result from a viral attack on the cochlear portion of the nerve, causing degeneration of cochlear neurons, along with sudden and severe hearing loss. Furthermore, neuropathy as a result of insulin deficiency is common in diabetes mellitus patients and can cause vestibular pathologies and retrocochlear hearing loss. Auditory neuropathy is a CN VIII pathology, which results in a loss of synchrony of neural firing (Berlin et al., 2001). The exact cause of auditory neuropathy/ dys-synchrony is often unknown, however the integrity of the AN can be affected by lack of auditory input to the cochlea, as in cases of severe to profound sensorineural hearing loss, resulting in neural degeneration (Musiek & Baran, 2007).

Surgical Injury to Auditory Nerve

Aside from infection and disease, trauma occurring during surgical procedures is a source of damage to CN VIII. AN compromise during surgery can take place by way of direct injury to the internal auditory artery or labyrinthine artery or by stretching or compression of CN VIII itself. Direct trauma can also result from drilling as well as transection of CN VIII. Thermal injury can further result by cautery or laser use during surgery (O'Malley et al., 2006). While most of the CN VIII pathologies discussed above cannot be predicted or prevented, surgical injuries are unique CN VIII pathologies because they are largely preventable with proper NIOM.

Auditory Evoked Potential Recording Tests employed in NIOM

NIOM of AN integrity during surgery can be done using a variety of evoked potentials techniques. When large numbers of AN fibers fire synchronously, evoked potentials can be recorded from the AN. By delivering an abrupt acoustic stimulus, the auditory system's response is generated as a series of neuroelectrical responses. Auditory evoked potential recordings can be obtained using near-field electrodes placed on or close to the AN or using far- field electrodes placed on the head (Musiek & Baran, 2007). The earliest responses occur within the first 10 milliseconds and are considered short-latency auditory evoked responses (Zamel, 2010). These responses can be recorded from the vicinity of the cochlea using electrocochleography (EcochG), at the level of the auditory brainstem using the ABR recorded from electrodes placed on the scalp, or by direct recording of the compound action potential (CAP) from the CN VIII while it is exposed during surgery (Møller, 2006).

Electrocochleography (EcochG)

EcochG is a technique of measuring electrical potentials generated within the cochlea and can be performed for NIOM by placing electrodes at the tympanic membrane or trans-tympanically within the middle ear space (Schlake et al., 2001; Zamel, 2010). The trans-tympanic method is used commonly for auditory monitoring in vestibular schwannoma resection procedures (Levine et al., 1978; 1984). Changes observed in EcochG potentials can imply that blood supply to the ear has diminished due to labyrinthine artery damage, at which point monitoring can no longer prevent permanent hearing damage. Also, because the EcochG

potentials reflect only the action potentials of the distal portion of the AN fibers, and the risk of damage in these surgical procedures lies in the intracranial portion of the nerve, monitoring by way of EcochG is limited in its usefulness (Møller, 2011).

Auditory Brainstem Response (ABR)

The ABR includes the actions potentials of the AN fibers (Wave I of the ABR) and adds several components that arise from later auditory brainstem structures. The remaining responses all typically occur within the first 10 milliseconds and reflect the conduction of stimuli through auditory pathways, as well as convey valuable information concerning the general function of the brainstem. The brainstem is comprised of three structures, each serving specific functions vital to survival. The brainstem is responsible for regulating respiration, heart rate and blood pressure, all of which remain fundamental to organism survival. An impaired brainstem can mean death for a patient. Therefore, monitoring of the brainstem during surgical procedures proves to be essential in maintaining the status of the living patient (Bhatnagar, 2008).

The auditory portions of the brainstem represent physiologically-accessible points that can be monitored relatively easily and non-invasively. The ABR consists of a series of peaks, labeled as waves, which are thought to originate from specific generator sites within the the peripheral auditory system and the brainstem. Waves I and II originate from the AN, Wave I from the more distal portion of CN VIII, and Waves III-V are generated as a result of neural functioning from the level of the brainstem (Møller & Jannetta, 1982; Møller et al., 1981). The brainstem plays a crucial role in the auditory system. Located within the brainstem are three groups

of nuclei that convey auditory information from the AN to higher regions of the central auditory nervous system (CANS). The first location within the CANS is the cochlear nucleus (CN). The CN is located in the caudal pons (Musiek & Baran, 2007). The cells of the CN preserve the neural firing pattern of the AN (Pfeiffer, 1966) therefore maintaining frequency representation. The CN's neurons can fire at high rates allowing for precise temporal coding ability. With respect to evoked potentials, the CN contributes to Wave III of the ABR, which occurs approximately 2 milliseconds after Wave I. Wave III has a relatively large amplitude in normal hearing patients (Møller, Jannetta, & Jho, 1994).

The next major group of auditory nuclei in the brainstem is located deep within the pons and makes up the superior olivary complex (SOC). Like the CN, a tonotopic arrangement of auditory nuclei is carried on through the SOC. Furthermore, the SOC is the first place in the auditory system in which auditory input is represented bilaterally. At this point, ipsilateral acoustic input can cross over permitting the comparison of contralateral and ipsilateral auditory input. These complex comparisons of temporal and intensity information then allows for key functions of the SOC, such as fusion, lateralization, and localization to be carried out. Fusion involves combining and integrating acoustic information arriving at both ears. The SOC is also highly sensitive to interaural time and intensity differences, providing the basis for lateralization and localization abilities of the auditory system (Musiek & Baran, 2007). In regards to the ABR waveform, the SOC contributes a strong response, which is believed to form Wave IV of the ABR (Møller et al., 1995).

The third group of auditory nuclei located throughout the auditory pathway in the brainstem is the lateral lemniscus (LL). This group of nuclei is located in the upper pons (Musiek & Baran, 2007). The tonotopic arrangement of the LL is not well understood, however it is known that the LL is sensitive to time and intensity differences and may contribute to localization abilities (Brugge, Anderson, and Aitkin, 1970). In reference to the ABR, the LL is a key contributor. It is known that the lateral lemniscus is the generator site mostly responsible for Wave V of the ABR (Møller, 2000).

The latencies and amplitudes of ABR waves are sensitive to physical injury to the structures that generate them. During surgical manipulation, it is mainly changes in latency values of the ABR wave components or the CAP from the AN that are used as evidence of CN VIII injuries. Amplitude changes in the ABR waveform are also red flags indicating surgically-induced injuries (Hatayama & Møller, 1998). During ABR monitoring, thorough and cautious assessment in the recordings for ABR pattern changes and their relationship to the surgical maneuvers being done are used in determining whether damage is being done or already occurred to the AN or brainstem (Zamel, 2010).

While interpretation of the ABR is complex, changes in CAP recordings taken directly from CN VIII can offer more exact, targeted evidence of AN impairment from surgical injury. ABR recordings during surgery must be compared to baseline recordings in the same patient performed preoperatively (Møller, 2011). Therefore, direct recording of the CAP provides advantages over ABR recordings in that it

allows for instantaneous feedback for changes occurring in the condition of the AN (Zamel, 2010).

According to the American Clinical Neurophysiology Society (2006) criteria, monitoring standard auditory evoked potentials involves the monitoring of the two main variables of latency and amplitude. Absolute latencies and interpeak intervals are the most reliable parameters used in the monitoring of the ABR, and interpretation of Waves I, III, and V are considered the most reliable peaks within the waveforms. Wave V is predominately the easiest wave to identify. Thus, changes in this wave's absolute latency, as well as changes in the Wave I-V interpeak interval are generally used to predict hearing loss during surgery.

Latency and amplitude values obtained throughout surgery are continuously compared using the same acquisition and stimulus parameters to the patient's own baseline ABR completed prior to the surgery (Zamel, 2010). Although there is no standard, the most commonly used latency criteria for warning the surgeon of possible CN VIII damage is a 1 millisecond delay in Wave V latency (Watanabe et al., 1989; Manninen et al., 1994). Alternative criteria include the complete disappearance of Wave V as an indication of possible hearing loss (Grundy et al., 1983; Friedman et al., 1995; Schlake et al., 2001) or a delay in Wave V of only 0.5 milliseconds or more (Coletti et al., 1998). James and Husain (2005) suggest that the criteria used to interpret Wave V latency changes should be done on an individual basis depending on the underlying pathology and the type of surgery. The lack of universal guidelines for interpreting latency changes is well recognized and acceptable due to the possibility of rigid criteria leading to unnecessary

warnings to the surgeon. However, it remains of utmost importance to notify the surgeon when steady decline of the waveform or latencies occurs even if the latency threshold criteria are not met (Zamel, 2010).

Unlike latency values, measures of peak amplitude vary considerably between patients. Therefore, amplitude of a waveform peak alone is not used as a criterion to interpret possible hearing loss during surgery (Zamel, 2010). In NIOM, ABR Wave amplitudes remain relatively consistent within the same patient (Zamel, 2010), however, the ratio of amplitudes of Waves V/I has been shown to be more constant (Tusa et al., 1994) than individual peak amplitudes, and amplitude ratio of Waves V/I has been shown to indicate injury to auditory pathways earlier or without any change in latency values. Likewise, Hatayama and Møller (1998) found amplitude of Wave V to be more sensitive at identifying hearing loss than latency. Criteria used for amplitude include a greater than 50% drop in Wave V amplitude, while others have argued that only a complete disappearance of Wave V can be a predictor of hearing loss (James & Husain, 2005).

Middle and Long-latency Auditory Evoked Potential Responses

Middle and long-latency auditory potentials are also produced in response to brief acoustic stimuli. The Auditory Middle Latency Response (AMLR) has a latency of 10 to 50 milliseconds and consists of three main positive and negative components, or peaks: Na, Pa, and Nb, with a second positive peak, Pb, sometimes present. The AMLR is the auditory evoked potential most commonly used to measure the effects of anesthesia and is highly sensitive to anesthetic agents, which is why this auditory evoked potential is not routinely used for clinical

neurophysiologic monitoring (Zamel, 2010). Succeeding the AMLR are late or long-latency auditory potentials. These evoked responses are mainly generated at the level of the cerebral cortex also making them exceptionally vulnerable to the effects of anesthesia. Because of this, later cortical responses, along with AMLR are not appropriate for the purposes of NIOM (Zamel, 2010).

Chapter 3: Types of Anesthesia and Associated Mechanisms of Action

In order to appreciate the effects of anesthesia on the ABR and other auditory evoked potentials, an explanation of the various types of sedatives and anesthetics and the mechanisms by which each operates is warranted.

Sedation versus Anesthesia

Depending on the type and goal of the procedure being performed, sedation, anesthesia, or a combination of both are induced in the patient. Sedation involves the depression of the central nervous system to generate relaxed and diminished responsiveness without inducing sleep and maintaining a particular level of consciousness (Elrich & Schroeder, 2012). Contrary to sedatives, anesthesia involves the absence of normal sensation, particularly that of pain by producing a level of unconsciousness sufficient to suppress the awareness of the surgical procedure (Smith, 1994).

From the perspective of NIOM, sedation may be used in conjunction with anesthesia during major surgical procedures in order to reduce the amount of noxious anesthetics used in a balanced anesthesia method (Zaviska, 1994). However, from a diagnostic audiologic standpoint, sedation is mainly used in the application of ABRs when reliable results in the measurement of hearing sensitivity cannot be obtained through traditional behavioral methods (Avlonitou et al., 2011;

Pillion et al., 2010). Sedation is used in populations including infants, young children (Avlonitou et al., 2011), and individuals with developmental disabilities to reduce myogenic activity that can interfere with the auditory evoked potential recording (Pillion et al., 2010). Sedated ABRs can be performed in clinical settings or the operating room with an anesthesiologist present. During surgical procedures for which NIOM is employed, sedatives such as barbiturates and benzodiazepines are used as an adjunct to anesthetics and analgesics. Conversely, for diagnostic sedated ABRs, chloral hydrate is widely used as an oral sedative hypnotic in pediatric and developmentally disabled populations (Avlonitou et al., 2011).

Types of Anesthesia

Anesthesia may be applied topically, regionally, locally, or generally. Topical anesthesia serves to numb only the tissue surface and can be used in the form of a liquid, ointment, or spray. Regional anesthesia involves the temporary interruption of neural conduction and is induced by injection of an anesthetic near the nerves to be blocked. Spinal and epidural anesthesia are examples of regional anesthesia. This type of anesthesia provides numbness while the patient maintains consciousness. Local anesthesia causes a loss of sensation within a restricted area, and like regional anesthesia, is produced by injection of an anesthetic near the target area (Elrich & Schroeder, 2012). Local anesthetics include lidocaine, bupivacaine, cocaine, and tetracaine. This type of anesthesia is often used during

minor surgeries on the oral cavity, which require peripheral nerve block in which only the surgical site is anesthetized and conscious sedation is maintained (Rassias & Procopio, 2003). Local and regional anesthetics are not commonly utilized during auditory surgeries.

General Anesthesia

For the purpose of major surgical procedures, including most procedures affecting the AN or CANS where NIOM takes place, general anesthesia is utilized. General anesthesia entails a total loss of bodily sensation and consciousness. General anesthesia functions to provide unconsciousness, amnesia, analgesia, and muscle relaxation, while maintaining homeostasis of physiologic function during surgery. General anesthesia can be induced by means of inhalation or intravenous injection. Inhalational anesthetic agents exist as either gases or volatile liquids, which readily evaporate to gaseous form. The gas or vaporized liquid is combined with oxygen from a compressed gas cylinder in an anesthesia delivery machine, and then routed to the patient through a breathing mask or cone. Gases include nitrous oxide and cyclopropane. Among the volatile liquids used are halothane, enflurane, isoflurane, sevoflurane, and desflurane. General anesthetics can also be administered intravenously or intramuscularly in liquid form. Propofol is commonly administered intravenously, and ketamine and xylazine are regularly given intramuscularly. These three agents are also frequently used in testing of the

auditory system in animals for experimental or clinical veterinary purposes. In addition, adjuvant intravenous agents are used intraoperatively for pain control. These anesthetic- enhancing narcotic agents include opioids, such as morphine, demerol, vicodin, codein, nubain, and fentanyl, the most common opioid used clinically in the United States (Rassias & Procopio, 2003). Neuromuscular blocking agents (NMBA) are also used in conjunction with inhaled and intravenous anesthetics, acting as sedatives to further prevent voluntary and reflex muscle movement during surgical procedures (Moore & Hunter, 2001). Neuromuscular blocking agents include pancuronium, atracurium, mivacurium, and vecuronium (Zavisca, 1994).

The ideal anesthetic agent would induce minimal cardiovascular and respiratory disruptions, would permit adequate oxygenation, and be nontoxic (Zavisca, 1994). However, this is not the case with many important anesthetics. Many frequently utilized anesthetic agents have been known to cause myocardial depression, respiratory and cardiovascular depression, hepatotoxicity, and renal toxicity. Nitrous oxide is a powerful analgesic with minimal cardiovascular effects. Therefore, the addition of nitrous oxide to the anesthetic regiment being used allows for a decreased need of the more toxic agent, while still producing the same pain relieving effects. Nitrous oxide is less soluble in tissues and allows for a more rapid awakening process for the patient. Also, the use of added NMBAs, small

amounts of opioids for additional analgesia, and benzodiazepines for additional sedation and amnesia can reduce the amount of toxic anesthetic needed. This technique is called balanced anesthesia (Zavisca, 1994).

Stages of Anesthesia

Galloway (2010) defined four stages of general anesthesia. Galloway described a patient undergoing general anesthesia as passing through each distinct stage smoothly with the introduction of various anesthetic agents (2010). The first stage is *premedication*, which serves to relieve the patient of anxiety and help the patient relax. The premedication stage employs the use of intravenous benzodiazepines, such as versed, or can include a narcotic, such as morphine or fentanyl for pain. The second stage is *induction*. Induction of anesthesia is done using an intravenous bolus of sedative and hypnotic agents. Often times, an intravenous opioid and neuromuscular relaxant or paralytic agent are administered. Monitoring of evoked potentials is likely to be avoided during this stage due to a bolus of anesthetic being likely to cause smaller amplitude cortical responses, rather than a lessened anesthetic effect seen with controlled infusions of anesthetic agents as observed in the third stage of anesthesia. The third stage is the *maintenance* of anesthesia. The maintenance stage makes up the majority of the surgical procedure. To sustain an anesthetic state throughout surgery, ongoing sedative hypnotic agents are used in conjunction with a volatile anesthetic or nitrous oxide in combination

with an opioid agent. The fourth and final stage is *emergence* from anesthesia. Emergence is carried out by lessening the amount of the volatile agent and introducing oxygen for the reversal or wearing off of the volatile agent.

Each pharmacologic agent used in the induction and maintenance of sedation and anesthesia produces different effects on the body, specifically the central nervous system. Failure of synaptic transmission, and thus delayed nerve conduction caused by these various drugs, can be observed at the level of the CANS and measured by the audiologist during sedated ABR testing and auditory evoked potential recordings intraoperatively.

Chapter 4: Non-anesthetic Variables that Influence Auditory Evoked Potentials in Neurophysiologic Intraoperative Monitoring

Anesthetic drugs and surgical injuries that affect the auditory nervous system are not the only likely cause for ABR waveforms to deviate from clinical norms. Age, gender, and temperature effects on ABR amplitude and latency have been well documented.

Age Effects

ABR absolute and interpeak latencies are longer for the newborn and infant populations. Adult-like latency values are not achieved until approximately two years of age (Hecox & Galambos, 1974; Salamy, 1984). For this reason, age-specific normative data are used by clinicians when interpreting ABR waveforms within this population (Gorga et al., 1989; Issa & Ross, 1995). Conversely, decreases in ABR amplitude and increases in latencies are commonly seen within the aging population (Jerger & Hall, 1980). Because age-related changes can result in demyelination or reduced numbers or of neural structures within the ABR generators, the cochlea, AN and auditory brainstem, neural conduction time can increase and neural synchrony can decrease. Therefore, AN input and temporal processing at these levels can be compromised (Austin et al., 2012). Moreover, age effects are also present in

response to anesthetic agents administered during ABR testing. The geriatric population is more sensitive to anesthetic agents overall. Lower amounts of anesthetic drugs are often required for older individuals to achieve similar effects that occur in younger individuals. Effects of anesthetic drugs are also usually prolonged in older patients as compared to younger patients (Kanonidou & Karystianou, 2007).

Gender Effects

Gender effects on the ABR have also been consistently reported. Adult females tend to exhibit ABRs with shorter absolute latencies, especially for later peaks, shorter interpeak latencies and larger response amplitudes compared to adult males (Dehan & Jerger, 1990). The etiology of this observed gender difference has been attributed to a combination of head size differences, hormonal effects on neural transmission (Dehan & Jerger, 1990), better hearing sensitivity on average for females (Corso, 1963), and higher average body temperature in women (Elkind-Hirsh et al., 1992). Decreased ABR latencies have been observed in the female during periods of increases in the natural female steroid, estrogen, also shown to increase basal body temperature, during the menstrual cycle by speeding up neural conduction within the female (Elkind-Hirsh et al., 1992). Differences in physical dimensions of the skull between males and females, with females having a smaller skull size on average, equate to less physical area for an evoked electrical response to travel, resulting in auditory evoked potentials observed at earlier latencies in females (Dehan & Jerger, 1990).

Not only have gender differences been observed in ABR recordings, gender effects have been associated with differences in response to the anesthetic state in general (Gan et al., 1999; Myles et al., 2001). Females have a higher body fat percentage and decreased water content compared to males, which affect the volume of distribution of many drugs (Pleym, 2003). Several studies have failed to report clinically relevant gender differences for inhalational anesthetics such as isoflurane and halothane (Coetzee & Stewart, 2002; Katoh et al., 1993), sevoflurane (Katoh et al., 1993; Sarton et al., 1999), and desflurane (Greif et al., 2002). However, gender effects have been reported for intravenous anesthetics such as propofol (Myles et al., 2001; Gan et al., 1999; Vuyk et al., 2001), opioid analgesics (Burns et al., 1989; Sidebotham et al., 1997; De Kock & Scholtes, 1991), and muscle relaxants (Semple et al., 1994; Donati & Bevan, 1999; Xue et al., 1997). Studies have reported males to be more sensitive than females to propofol (Myles et al., 2001; Gan et al., 1999; Vuyk et al., 2001), and decreasing the propofol dose by 30-40% when administered to males has been suggested in order to accomplish similar recovery times in males and females. Studies have also shown females to be 20-30% more sensitive to the effects of the muscle relaxants vecuronium (Semple et al., 1994), pancuronium (Donati & Bevan, 1999), and rocuronium (Xue et al., 1997). Similarly, research on gender differences in response to opioid analgesics has shown females to be more sensitive than males to opioids, particularly morphine (Burns et al., 1989; Sidebotham et al., 1997; De Kock & Scholtes, 1991). Therefore, males are required to receive 30-40% higher doses of opioid analgesics than females to attain the same pain relieving effects (Pleym, 2003).

Temperature Effects

Additionally, body temperature changes caused by anesthesia during surgery have been associated with increased ABR latencies. Anesthesia can cause vasodilation, which can then lead to decreased core body temperature and slow neural conduction time, resulting in increased ABR interpeak latencies (Markand et al., 1987). Physiologic events that can occur during surgical procedures have also been shown to affect the ABR. Local or systematic hypothermia can cause prolonged absolute and interpeak latencies and also wave amplitudes to diminish. Tissue compression and retraction can lead to abolished or degraded averaged auditory responses. In addition, insufficient ventilation, hemodilution, systemic hypotension and regional ischemia can produce reduced oxygen effects on the endocochlear potential by causing decreased cochlear output (Edwards & Kileny, 2005).

Chapter 5: Effects of Specific Anesthetic Agents on Auditory Evoked Potential Recordings

A great deal of literature has investigated anesthetic and sedative effects on auditory evoked potential recordings. The most common agents used throughout this literature are members of the general anesthesia family of volatile liquids, including isoflurane, sevoflurane, enflurane, and nitrous oxide, along with those most commonly used in animal studies, ketamine and xylazine, which are administered as intramuscular solutions. General inhalation anesthetics, such as isoflurane, sevoflurane, enflurane, and nitrous oxide are often used because they demonstrate rapid induction and quick recovery time with little residual effects. Using inhalation anesthesia also provides the advantage of more precise regulation by allowing more immediate adjustment of the anesthetic level when the physiologic state of the human or animal is altered. Ketamine and xylazine, however, require an induction time of several minutes and recovery time of several hours. Furthermore, equipment for the administration of inhalation anesthetics is costly and waste gases can pose a hazard to laboratory or surgical environments and should be vented from these environments. Equipment for the administration of ketamine and xylazine is less costly, but the use of a hypodermic needle and syringe requires more training for laboratory personnel (Ruebhausen et al., 2012). Several studies to date have looked at the influence of various anesthetic agents on

auditory evoked potentials, specifically the ABR. Some studies have found that halogenated anesthetic agents affect the ABR in animals (Van Looij et al., 2004), as well as humans (Edwards & Kileny, 2005), while other study data have suggested that these agents cause prolongation of latencies of ABR components only at high concentrations (Galloway, 2010). Other studies (Møller, 2011; Edwards & Kileny, 1997) have found no effects on the ABR by this group of anesthetics. According to an article published by Stronks and colleagues (2010), general anesthetics, such as barbiturates (Shapiro et al., 1984; Drummond et al., 1985; Church & Shucard, 1987), ketamine (Church & Gritzke, 1987), and the halogenated volatiles (Dubois et al., 1982; Sainz et al., 1987; Santarelli et al., 2003) typically increase ABR latency, especially that of the later peaks, and do not typically affect ABR amplitude, whereas nitrous oxide (Manninen et al., 1985) and the opioids, such as morphine and fentanyl (Samra et al., 1984) do not alter the ABR. A detailed discussion of the effects of different anesthetics on auditory evoked potentials in humans and animals follows:

Barbiturates

Barbiturates are a class of drugs which function to depress the central nervous system and can be used as sedatives, hypnotics (sleep-inducing), and anticonvulsants to prevent seizures (Elrich & Schroeder, 2012). Examples of barbiturates include thiopental, phenobarbital, and pentobarbital. Studies by Stockard et al. (1977) and Duncan et al. (1979) both found barbiturates to have no influence on ABRs in humans. A later study by (Newlon et al., 1983) also stated that barbiturate agents do not influence human ABRs. Conversely, the barbiturate

pentobarbital was shown to increase CAP thresholds and latencies at high stimulus frequencies (Cazals et al., 1980). Pentobarbital has also been reported to decrease cochlear microphonic (CM) amplitudes (Samara & Tonndorf, 1981). Furthermore, pentobarbital in amounts greater than 9 mg/kg has been found to cause prolonged ABR latencies and reduced ABR amplitudes and the barbiturate agent thiopental has been shown to prolong Wave V latencies and reduce ABR amplitudes in doses greater than or equal to 20 mg/kg (Edwards & Kileny, 2005).

Halothane

Halothane is a volatile synthetic organic compound used as an inhalational general anesthetic. Stockard et al. (1977) reported that halothane had no influence on ABRs in humans, and Duncan et al. (1979) reported that no effects of halothane were found in ABRs from children. However, James et al. (1982) found that the use of halothane increased ABR latencies in adults.

Nitrous Oxide

Nitrous Oxide is a chemical compound in the form of a gas at room temperature, and is also commonly known as laughing gas. It is used as an adjunct to general anesthesia for its analgesic effects (Zavitsa, 1994). Several studies have examined the effects of the addition of nitrous oxide to various concentrations of halogenated volatile anesthetics. Manninen et al. (1985) studied the effects of the addition of 50% nitrous oxide to isoflurane anesthesia in humans. This study found that the addition of the nitrous oxide compound had no effect on ABRs. These results are consistent with a previous study, reporting no change in latency with addition of

70% nitrous oxide to enflurane anesthesia in normal hearing patients (Rosenblum et al., 1982).

Halogenated volatiles

The effects of isoflurane on the ABR have been well documented. Several studies on isoflurane effects in humans have shown increased latency of late ABR peaks, however the ABR amplitude was unaffected (Manninen et al., 1985; Sebel et al., 1986; Lloyd-Thomas et al., 1990). Manninen et al. (1985) studied the effects of isoflurane on the ABR in 10 healthy adults. This study found isoflurane to increase the absolute latencies of Waves III, IV, and V significantly above awake control levels. Manninen et al. (1985) also found that interpeak latencies were significantly increased as well. The increase occurred at 1.0% end-tidal isoflurane and did not continue to further increase after 1.5% and 2.0% end-tidal isoflurane concentration. Edwards and Kileny (2005) report a general delay of 0.5-1.0 ms prolongation of ABR Wave V, as well as an increased I-V interpeak latency when end-tidal concentration exceeded 1.5% for inhalation anesthetics including isoflurane, enflurane, and halothane.

Several animal studies have demonstrated increased latency and decreased amplitude effects on several ABR peaks after isoflurane administration (Santarelli et al., 2003; Stronks et al., 2010; Ruebhausen et al., 2012). Isoflurane was also reported to attenuate cochlear evoked responses in Guinea pigs (Stronks et al., 2010). This study found isoflurane dose-dependently suppressed the amplitude and latency of the CAP and suppressed CM amplitude at 2.5% and 3% end-tidal concentrations. These results are contradictory to those obtained in the

aforementioned Manninen et al. (1985) study, completed in a human population. The Manninen et al. (1985) study demonstrated a plateau effect, in which no further amplitude or latency delays were observed after 1.5% end-tidal concentration. This discrepancy can be possibly be attributed to differences in how the Guinea pig and human process isoflurane anesthesia. Additionally, a study by Ruebhausen et al. (2012) found that hearing thresholds obtained under isoflurane anesthesia were elevated approximately 27 dB on average across all stimuli compared to those obtained under ketamine/xylazine anesthesia.

Sevoflurane and enflurane, additional members of the halogenated volatile family have been used in studies of auditory evoked potentials. Thorton et al. (1983) found that enflurane was linked to increased ABR wave latencies, especially in Waves III and V. Norrix et al. (2012) retrospectively analyzed latencies of ABR in children given sevoflurane. Norrix and colleagues (2012) found ABR Wave I and III latencies to be very similar between the unanesthetized control and anesthesia groups, while Wave V latencies and interpeak intervals (I-III, III-V, I-V) for the anesthesia group were delayed compared to those of the control group.

Likewise, Dubois et al. (1982) studied effects of 1%, 2%, 3% enflurane on the human ABR. Results showed that enflurane consistently produced changes in latencies, waves most affected were Waves III, IV, and V, and the magnitude of the delay in latency was directly related to the concentration of enflurane, maximum at highest concentration of 3%, and reversing itself as the concentration decreased. Furthermore, the interpeak latencies were statistically different at concentrations of 2% and 3%, but not statistically different from control values at 1% enflurane or

when patient was waking up, even though they remained elevated. Amplitude effects were not statistically significant. Interestingly, Stockard & Brickford (1975) outlined the depressive effects of enflurane on the brainstem leading to cortical epilepsy. Additionally, animal studies have shown that ABRs may be modified by enflurane (Jones et al., 1978).

Ketamine & Xylazine

One study using ketamine anesthesia has shown that this agent does not alter ABR amplitude, only slightly increases latency, and has no effect on ABR thresholds (Smith & Mills, 1989). Another study using ketamine anesthesia reported an increase in CAP threshold and latency at high frequencies (Cazals et al., 1980). Further studies have reported ketamine to increase peak latencies in the gerbil and rat (Church & Gritzke, 1987; Smith & Mills, 1989, 1991). Additionally, Van Looij and colleagues found anesthesia with a ketamine/xylazine mixture caused a significant prolongation of ABR peak and interpeak latencies, as well as a significant increase in ABR thresholds as compared to the awake condition. Similarly, Reubenhause and colleagues (2012) found ABR latencies increased slightly in rat population under ketamine/xylazine anesthesia.

Chapter 6: Conclusion

Much of the work published on auditory evoked potentials and the effects of anesthetics (Dubois et al., 1982; Manninen et al., 1985; Norrix et al., 2012; van Looij et al., 2004; Stronks et al., 2010; Reubhausen et al., 2012), supports the finding that anesthetic agents, specifically those of the halogenated volatile family influence ABRs. However, some studies (reviewed by Møller, 2011) do not support this finding, instead finding that auditory evoked potentials at the level of the brainstem are impervious to this group of anesthetic agents. Animal research studies, including those by van Looij et al. (2004), Stronks et al. (2010), and Reubhausen et al. (2012), have found isoflurane and ketamine/xylazine anesthesia to affect auditory evoked potential thresholds, latencies (van Looij et al., 2004; Stronks et al., 2010), and amplitude (Stronks et al., 2010). Additionally, several studies in the human population, including those by Dubois et al. (1982), Manninen et al. (1985), and Norrix et al. (2012) have reported halogenated volatile anesthetics influencing ABR absolute and interpeak latencies.

Edwards and Kileny (1997) reported that volatile anesthetics may affect ABR Wave V or the I-V interpeak latency because of these anesthetic's ability to depress neural activity and cerebral metabolic rate. Furthermore, a review by Banoub et al. (2003) stated that the volatile anesthetics are associated with slight increases in

ABR latency due to the depressive affects of these anesthetics on neuronal activity. Banoub et al. (2003) point out that the volatile anesthetics slow synaptic neural transmission, with these effects being more pronounced on later cortical evoked potentials compared to brainstem evoked potentials. As for the middle latency responses, the AMLR, there is ample evidence that general anesthetics, especially those of the halogenated volatile family increase the latency and decrease the amplitude of the AMLR (Thorton & Sharpe, 1998; Goto et al., 2001)

Contradictory to these research findings, Møller (2011) states that subcortical auditory evoked potentials, including the ABR and CAP recorded from the exposed AN are not affected by commonly used anesthetics. Møller (2011) reports that although slight changes in ABR recordings have been found as a result of certain anesthesia (Cohen & Britt, 1982; Thorton et al., 1981), the ABR is notably insensitive to anesthetic agents. Møller (2011) goes on to state that any type of anesthesia can be considered without any regard to possible negative effects on ABR recordings. Edwards and Kileny (1997) state that the ABR is generally regarded to be resistant to effects of pharmacological agents.

Although a wealth of resources refute the fact that volatile anesthetics and other anesthetic agents negatively impact auditory evoked potential recordings, an abundance of literature has provided evidence of prolonged ABR latencies, decreased ABR amplitudes, and increased thresholds, as well as CAP threshold and latency increases and CAP amplitude decreases, and even decreases in the CM (Stronks et al., 2010). Because of the existence of such long-standing evidence to support anesthesia inducing effects on auditory evoked potentials, audiologists

should be cautious when interpreting ABR data during surgical procedures using general anesthesia.

Though only slight changes to ABR recordings have been reported, audiologists performing neurophysiologic intraoperative monitoring should be knowledgeable of the types and concentrations of pharmacological agents being administered to the patient and the effects of these drugs on the ABR in relation to the surgical procedure being performed. To this end, it is apparent that successful NIOM requires a team approach involving steady communication between members of the surgical, anesthesiology, and audiological NIOM teams (Galloway, 2010). Furthermore, successful NIOM commands the use of general anesthetics, which do not significantly alter electrophysiologic signals (Iwasaki et al., 2003) to allow for accurate and reliable interpretation. Therefore, the appropriate choice of anesthetic is critical and depends on the underlying medical condition of the patient, the type of surgical procedure taking place, and the type of monitoring necessary (Galloway, 2010).

In order for the NIOM audiologist to consider all of these factors and communicate his/her anesthetic preference to the anesthesiologist based on what the surgeon desires to be monitored, the audiologist must be well versed in pharmacological effects on the ABR. Accreditation in NIOM from two organizations, the American Board of Neurophysiologic Monitoring (ABNM) and the American Board of Registration of Electroencephalographic and Evoked Potential Technologists, requires testing in the area of anesthesia effects. For example, the written exam developed by the ABNM is broken down into basic neuroscience 30%,

signal acquisition and processing 8%, electroencephalography (EEG) 8%, sensory evoked potentials 24%, motor potentials 22%, and effects of anesthesia 8% (ABNM, 2012). Although the ABNM requires the studying audiologist to be proficient in several areas including the area of anesthesia and its effects on evoked potentials, they provide no single reference that can be used in preparation for the examination. Instead, the ABNM provides a list of 23 textbooks and 9 journals they recommend as references for study material. Aside from these publicly available materials, the ABNM does not sanction a specifically designed review course or study guide for the purpose of its accreditation exam (ABNM, 2012). For this reason, a single book of normative data in the area of anesthesia should be developed for the audiologist pursuing a career in NIOM to aid in the study of this portion of the examination. This book should consist of a review of the types and classes of anesthetic agents, and a list of those drugs that have been shown to influence auditory evoked potentials, including the ABR, as well as other sensory evoked potentials and motor potentials. This book should provide normative data of the effects for each drug listed, as well as separate norms accounting for the effects of gender, age, and body weight. This would include different populations, such as males versus females, children versus adults, and younger adults versus older adults. This book should also describe the effects of additional physiological variables on evoked potentials, including hypothermia, hypotension, anoxia, and ischemia. Ultimately, this book should serve as a complete reference, with all relevant anesthetic data compiled in one place and should function as an aggregate source for audiologists and those alike whose goal is to practice NIOM. Overall,

audiologists have contributed greatly to the field of NIOM for many years and are well qualified due to the training they receive in electrophysiology, clinical data, and patient performance (Edwards & Kileny, 1998). Proficient knowledge of anesthetics and their effects on evoked potentials will strengthen the audiologist's claim to the profession of NIOM.

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